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Moe-Byrne T, Brown JVE, McGuire W

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Naloxone for opioid-exposed newborn infants.

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Naloxone for opioid-exposed newborn infants

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ABSTRACT

Background

Naloxone, a specific opioid antagonist, is available for the treatment of newborn infants with cardiorespiratory or neurological depression that may be due to intrauterine exposure to opioid. It is unclear whether newborn infants may benefit from this therapy and whether naloxone has any harmful effects.

Objectives

To determine the effect of naloxone on the need for and duration of neonatal unit stay in infants of mothers who received opioid analgesia prior to delivery or of mothers who have used a prescribed or non-prescribed opioid during pregnancy.

Search methods

We searched the following databases in February 2018: the Cochrane Central Register of Controlled Trials (the Cochrane Library 2018, Issue 1), MEDLINE (OvidSP), MEDLINE In process & Other Non-Indexed Citations (OvidSP), Embase (OvidSP), CINAHL (EBSCO), Maternity and Infant Care (OvidSP), and PubMed. We searched for ongoing and completed trials in the WHO International Clinical Trials Registry Platform and the EU Clinical Trials Register. We checked the reference lists of relevant articles to identify further potentially relevant studies.

Selection criteria

Randomised controlled trials comparing the administration of naloxone versus placebo, or no drug, or another dose of naloxone to newborn infants with suspected or confirmed in utero exposure to opioid.

Data collection and analysis

We extracted data using the standard methods of Cochrane Neonatal with separate evaluation of trial quality and data extraction by two review authors and synthesis of data using risk ratio, risk difference, and mean difference.

Main results

We included nine trials, with 316 participants in total, that compared the effects of naloxone versus placebo or no drug in newborn infants exposed to maternal opioid analgesia prior to delivery. None of the included trials investigated infants born to mothers who had used a prescribed or non-prescribed opioid during pregnancy. None of these trials specifically recruited infants with cardiorespiratory or neurological depression. The main outcomes reported were measures of respiratory function in the first six hours after birth. There is some evidence that naloxone increases alveolar ventilation. The trials did not assess the effect on the primary outcomes of this review (admission to a neonatal unit and failure to establish breastfeeding).

Authors' conclusions

The existing evidence from randomised controlled trials is insufficient to determine whether naloxone confers any important benefits to newborn infants with cardiorespiratory or neurological depression that may be due to intrauterine exposure to opioid. Given concerns about the safety of naloxone in this context, it may be appropriate to limit its use to randomised controlled trials that aim to resolve these uncertainties.

PLAIN LANGUAGE SUMMARY

Naloxone for opioid-exposed newborn infants

Review question

Does naloxone (a drug that counters the negative effects of opioids on breathing) help newborn babies whose mothers have received opioid pain relief during birth?

Background

When a woman receives opioid medicines for pain relief during labour (for example, pethidine, morphine, and similar drugs), the opioid can cross over to the baby inside the womb and then reduce the newborn baby's breathing rate. Naloxone, a drug that counters the effects of opioids, can be given to the newborn baby to try to prevent or treat problems with breathing. This may reduce the chance of the baby needing to go to a neonatal unit for help with breathing, and reduce the need for separating mother and baby (and so help with establishing breastfeeding). Concern exists, however, that naloxone may cause side effects, including possible long-term developmental problems.

Study characteristics

We found nine completed trials that compared giving to newborn babies, whose mothers had received opioids during labour, either naloxone or a placebo ('dummy drug'). These trials were conducted more than 30 years ago and they were generally very small including only about 300 infants in total. Most of the trials did not use reliable methods consistently. Evidence is up-to-date as of February 2018.

Key results

The trials reported the effects of naloxone on the baby's breathing but did not assess the effect on the need for babies to be cared for in a neonatal unit (separated from their mother), whether they needed help with breathing, or on breastfeeding success. None of the trials assessed long-term development. We did not find any trials including babies born to mothers who had used opioids (whether prescribed or non-prescribed) during pregnancy.

Quality of evidence

The available evidence was not sufficient to determine whether giving naloxone to babies whose mothers received opioids during birth was helpful or harmful.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Naloxone compared to placebo or no drug for opioid-exposed newborn infants						
Patient or population: opioid-exposed newborn infants Setting: Intervention: naloxone Comparison: placebo or no drug						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no drug	Risk with Naloxone drug				
Admission to neonatal intensive or special care unit - not reported	-	-	-	-	-	Primary outcome, not measured in the included trials
Duration of neonatal intensive or special care unit stay - not reported	-	-	-	-	-	Primary outcome, not measured in the included trials
Failure to establish breastfeeding prior to hospital discharge - not reported	-	-	-	-	-	Primary outcome, not measured in the included trials
Neurodevelopmental outcomes beyond infancy - not reported	-	-	-	-	-	Primary outcome, not measured in the included trials
Receipt of endotracheal intubation - not reported	-	-	-	-	-	Secondary outcome, not measured in the included trials

Receipt of assisted ventilation - not reported	-	-	-	-	-	Secondary outcome, not measured in the included trials
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***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

BACKGROUND

Description of the condition

Opioid analgesics are available, recommended, and commonly used for relief of maternal pain during labour in most birth settings in middle- and high-income countries (Jones 2012; NICE 2017). Estimates suggest that about one-third to one-half of women receive opioid analgesia in labour. The extent of use in lower-middle and low-income settings is less certain (Redshaw 2007; Ullman 2010), though likely to be less than in high-income countries (James 2012; Ogboli-Nwasor 2014).

The commonly used opioids (pethidine, diamorphine, morphine, fentanyl) are highly lipid soluble and transplacental transfer to the fetus occurs rapidly. Intrauterine exposure to maternal opioids within about four hours of birth may be associated with neurological and cardiorespiratory depression and feeding-behaviour problems in newborn infants (Kumar 2003; Mercer 2007; Reynolds 2010). Concern exists that these adverse effects may delay neonatal physiological transition and postnatal adaptation and result in neonatal unit admission and potentially separation of the infant and mother. Delay in establishment of effective breastfeeding is an important possible consequence of this maternal-infant separation (Burchell 2016; Nissen 1995; Ransjö-Arvidson 2001). Observational data from surveillance studies have suggested that infants who experience an acute life-threatening event in the early neonatal period or a sudden unexpected early neonatal death are more likely to have been exposed to maternal opiates during birth, but a causal link has not been established (Lutz 2016).

Description of the intervention

Naloxone, a specific “opioid antagonist” that blocks the actions of opiates on cells, is available for the treatment of neurological and cardiorespiratory depression in opioid-exposed newborn infants. The International Liaison Committee on Resuscitation (ILCOR) has provided guidance on the use of naloxone for newborn infants (Niermeyer 2001). The advice follows the long-standing recommendation of the American Academy of Pediatrics (AAP) Committee on Drugs that naloxone should not be used routinely in opioid-exposed newborn infants but should be “reserved for adjunctive therapy in selected infants who have not initiated or established independent respiration following ventilation, are significantly depressed, and have a high probability of being narcotized” (AAP 1980). These recommendations refer to infants of mothers who have received opioid for analgesia up to four hours prior to delivery. The dose of naloxone recommended in 1980, 0.01 mg/kg, was later revised to 0.1 mg/kg (AAP 1990). In 2010, an ILCOR Consensus on Science and Treatment Recommendations statement updated this advice and suggested that naloxone should only be given to infants with severe respiratory depression after

positive-pressure ventilation has restored a normal heart rate and colour (Kattwinkel 2010; Perlman 2010). Despite these guidelines, surveys of policy and practice indicate that clinicians continue to administer naloxone to opioid-exposed newborn infants in the first few minutes after birth even in the absence of neurological or cardiorespiratory depression or before effective supported ventilation is established (Herschel 2000; Gill 2007).

Opioid-dependent mothers

The AAP Committee on Drugs has advised that naloxone should not be administered to infants of opioid-dependent mothers as naloxone may precipitate acute withdrawal and seizures in opioid-habituated infants (Gibbs 1989; AAP 1998). There are few data on significant adverse events due to naloxone in infants of opioid-dependent mothers and some authors have recommended a small dose of naloxone (0.01 mg/kg) as a part of the resuscitation of such infants (Maas 1990).

Why it is important to do this review

Naloxone should not be regarded as harmless. Concern exists that naloxone may interfere with the role of the infant’s own natural opioids in programming metabolic, hormonal, and physiological processes (Smotherman 1992; De Castro 1993; Szeto 1995). Given these questions of appropriateness of use and potential long-term effects, it is important to evaluate the available data on the use of naloxone in opioid-exposed newborn infants.

OBJECTIVES

To determine the effect of naloxone on the need for and duration of neonatal unit stay in infants of mothers who received opioid analgesia prior to delivery or of mothers who have used a prescribed or non-prescribed opioid during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using either random or quasi-random patient allocation.

Types of participants

Newborn infants of any gestation with suspected or confirmed exposure to opioids, either:

1. as maternal pain relief prior to delivery;
2. as a result of use during pregnancy.

Types of interventions

Trials comparing naloxone with placebo or no drug, or comparing more than one dose of naloxone, as part of the management of newborn infants.

Types of outcome measures

Primary outcomes

Mother-infant separation, effect on breastfeeding, and neurodevelopment

1. Admission to neonatal intensive or special care unit;
2. Duration of neonatal intensive or special care unit stay;
3. Failure to establish breastfeeding by hospital discharge;
4. Neurodevelopmental outcomes beyond infancy assessed using validated assessment tools.

Secondary outcomes

Cardio-respiratory function, need for support, and neurobehavioural outcomes

1. Measures of respiratory function, such as Apgar score, or arterial blood pH, or arterial or alveolar carbon dioxide tension measured within the first six hours after birth;
2. Receipt of assisted ventilation (any form of mechanical ventilation including continuous positive airway pressure) in the neonatal period;
3. Receipt of endotracheal intubation for respiratory support;
4. Duration of assisted ventilation (days);
5. Duration of endotracheal intubation (days);
6. Days from birth to establish full oral feeds independently of parenteral fluids or nutrition or of enteral tube feeding;
7. Features of opioid withdrawal, using validated behavioural assessment measures in the neonatal period;
8. Seizures in the neonatal period.

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal.

Electronic searches

We updated the searches in February 2018 to identify reports of trials available since the searches in June 2012. The original search strategy from June 2012 was checked and updated ([Appendix 1](#)). We searched the following databases on 20 February 2018: the Cochrane Central Register of Controlled Trials (the Cochrane Library 2018, Issue 1), MEDLINE (OvidSP), MEDLINE In process & Other Non-Indexed Citations (OvidSP), Embase (OvidSP), CINAHL (EBSCO), Maternity and Infant Care (OvidSP), and PubMed. We imported the search results into reference management software and de-duplicated the results against the previous search results from June 2012. We did not apply any language restrictions. A search filter was applied in MEDLINE and Embase to limit retrieval to randomised controlled trials ([Lefebvre 2008](#); [Lefebvre 2011](#)).

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictpr/search/en/, the ISRCTN Registry, and the EU Clinical Trials Register <https://www.clinicaltrialsregister.eu/>). We were unable to search the metaRegister of Controlled Trials for this update as it is no longer available.

Searching other resources

We examined the references in studies identified as potentially relevant for other eligible studies. We also searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2018), the European Society for Pediatric Research (1995 to 2017), the UK Royal College of Paediatrics and Child Health (2000 to 2018) and the Perinatal Society of Australia and New Zealand (2000 to 2017). We considered trials reported only as abstracts to be eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

Two review authors independently screened the title and abstract of all studies identified by the above search strategy. We assessed the full text of any potentially eligible reports and excluded those studies that did not meet all of the inclusion criteria. We discussed any disagreements until consensus was achieved.

Data extraction and management

We used a data collection form to extract relevant information from each included study. Two review authors extracted the data

separately. We discussed any disagreements with the third review author until we reached consensus.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017). Any disagreements were resolved by discussion or by a third assessor. See Appendix 2 for a description of risk of bias for each domain assessed.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CI) using RevMan 2014 software. When it was deemed appropriate to combine two or more study arms, we obtained the treatment effects from the combined data using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster-randomised RCTs. For cluster-randomised RCTs, we planned to undertake analyses at the level of the individual while accounting for the clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We requested outcome data from the trial investigators when these were unavailable in the report.

Assessment of heterogeneity

Two authors assessed clinical heterogeneity, with a meta-analysis conducted only when both authors agreed that study participants, interventions, and outcomes were sufficiently similar. We examined the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and described the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high heterogeneity ($I^2 > 50\%$), we would explore the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

We intended to conduct a funnel-plot analysis if there were data from more than 10 trials included in a meta-analysis.

Data synthesis

We used fixed-effect models for meta-analysis (as per Cochrane Neonatal recommendations). Where moderate or high heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence for the primary outcomes and key secondary outcomes we considered most relevant to parents and caregivers (Schünemann 2013; Appendix 3):

1. Admission to neonatal intensive or special care unit;
2. Duration of neonatal intensive or special care unit stay;
3. Failure to establish breastfeeding by hospital discharge;
4. Neurodevelopmental outcomes beyond infancy;
5. Receipt of assisted ventilation;
6. Receipt of endotracheal intubation.

Two authors independently assessed the quality of the evidence for each of these outcomes. We considered evidence from randomised controlled trials initially as high-quality but downgraded this evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

1. dose of naloxone < 0.1 mg/kg body weight;
2. dose of naloxone ≥ 0.1 mg/kg body weight.

Sensitivity analysis

We planned sensitivity analyses to determine if the findings were affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and $< 10\%$ loss to follow-up.

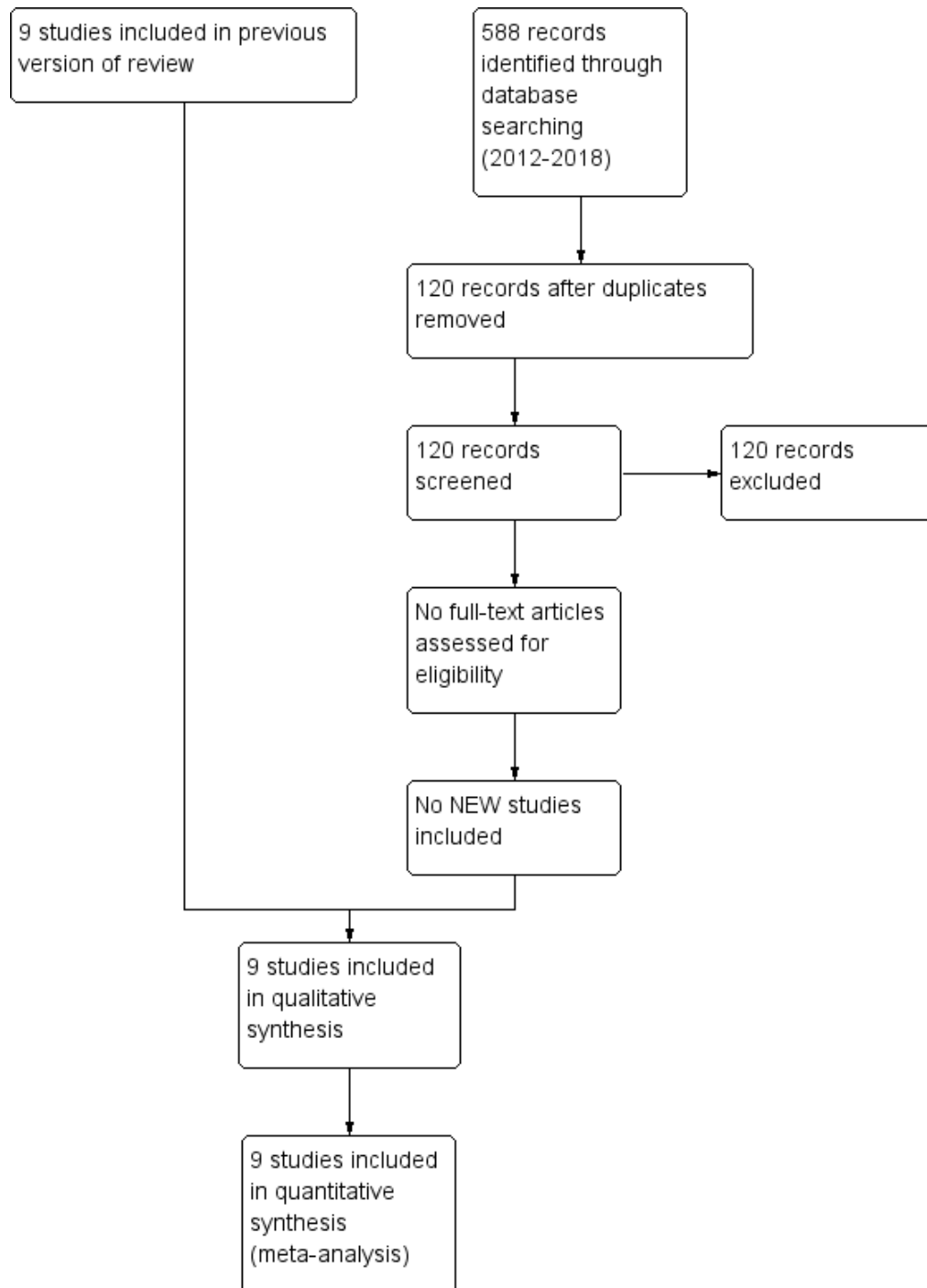
RESULTS

Description of studies

Results of the search

The update search returned 588 records. After de-duplication, 120 titles and abstracts were screened. The records that did not meet the inclusion criteria were excluded at title and abstract screening, and no studies were ordered for full-text screening. The study selection process is illustrated in [Figure 1](#). We did not identify any planned or ongoing studies.

Figure 1. Study flow diagram: review update



Included studies

We included nine trials and these are described in the table 'Characteristics of included studies'. Two of these were reported in the same article (Dick 1978a; Dick 1978b).

A total of 316 infants participated in the included trials. All were undertaken in the 1970s or early 1980s. The participants were term newborn infants whose mothers had received pethidine (meperidine) for pain relief up to six hours prior to delivery. None of the trials specifically restricted participation to infants with cardiorespiratory or neurological depression following opioid exposure. In most trials, the intervention appears to have been given in the first five minutes after birth. In two trials, naloxone was given later; at 30 minutes (Gerhardt 1977) or at one hour (Welles 1984) after birth. Naloxone was administered via the intramuscular route in four trials, and in the other five via the umbilical venous route. The dose of naloxone used ranged from 0.01 to 0.07 mg/kg with the exception of one study in which a total dose of 0.2 mg was given (Wiener 1977b). The outcomes most commonly assessed were measures of respiratory effort such as Apgar scores, blood gases values, or other measures of alveolar ventilation.

None of the trials examined the effects of naloxone in infants of mothers who had used a prescribed or non-prescribed narcotic during pregnancy.

Excluded studies

We excluded two studies (Martin 1972; Brice 1979b; see Characteristics of excluded studies).

Risk of bias in included studies

All of the trials were small and none presented a sample size calculation. The 'Risk of bias' assessment was hampered by incomplete reporting of trial methods (most likely due to the studies pre-dating current reporting guidelines). Across included studies, several 'Risk of bias' domains had to be assessed as 'unclear' as details were not reported in the publications.

Allocation

Three studies reported adequate measures of allocation concealment and random sequence generation, reducing the risk of selection bias in these trials. The remaining six reports did not provide sufficient details of measures to ensure allocation concealment or random sequence generation.

Blinding

Caregivers or assessors were likely to have been blinded in five of the trials. Three trials reported that outcome assessors were unblinded and in one trial it was unclear whether outcome assessors were blinded.

Incomplete outcome data

All of the trials appear to have achieved complete or near-complete follow-up of infants recruited although none of the trials undertook follow-up beyond the first three days after birth.

Selective reporting

The risk of reporting bias was unclear across the included studies as trial protocols were not available (most likely due to the age of the studies). However, for eight of the nine included trials, there was no reason to suspect selective reporting.

One trial was considered to be at high risk of selective reporting as the paper stated that certain outcomes (including one primary and one secondary outcome) would not be reported in the publication but would be available from the corresponding author. Due to the age of the study, we were unable to make contact with any of the authors and were, hence, unable to access these data despite knowing that they were collected during the trial.

Other potential sources of bias

In seven out of nine included studies, no other potential sources of bias were identified and the risk of other bias was, consequently, judged to be low. One study was stopped early because the randomisation code was broken. However, further details pertaining to the causes of this breach of protocol or its consequences were not discussed in the paper. One other study was reported to have been funded by the pharmaceutical company that manufactured the intervention. Both these trials were judged to have an unclear risk of other biases.

Effects of interventions

See: [Summary of findings for the main comparison](#) Naloxone compared to placebo or no drug for opiate-exposed newborn infants

Primary outcomes

Admission to neonatal intensive or special care unit:

Not reported.

Duration of neonatal intensive or special care unit stay:

Not reported.

Failure to establish breastfeeding by hospital discharge:

Not reported.

Neurodevelopmental outcomes beyond infancy assessed using validated assessment:

Not reported.

Secondary outcomes

Measures of respiratory function:

Eight of the trials presented data on measures of respiratory function measured within the first six hours after birth. There were no statistically significant differences in the Apgar score (Bonta

1979), respiratory rate (Evans 1976), time to sustained respiration (Brice 1979a), minute ventilation (Gerhardt 1977), or blood gas parameters (Bonta 1979; Dick 1978a; Dick 1978b).

Four trials assessed measures of alveolar ventilation (Brice 1979a; Evans 1976; Wiener 1977a; Wiener 1977b). At 30 minutes and four hours post intervention, the expired carbon dioxide output and alveolar ventilation rate were statistically significantly higher, and the alveolar carbon dioxide tension lower, in the naloxone group (Analysis 1.1; Analysis 1.2; Analysis 1.3; Figure 2; Figure 3; Figure 4). We detected statistical heterogeneity in analysis 1.2 (alveolar carbon dioxide tension) and analysis 1.3 (alveolar ventilation). In each analysis (alveolar carbon dioxide tension at 30 minutes (1.2.2) and at four hours (1.2.4) and alveolar ventilation at 30 minutes (1.3.3) and at four hours (1.3.5)), the heterogeneity arose from the same study (Wiener 1977b). This study used a larger dose of naloxone, and naloxone was given intramuscularly compared with intravenously in the other studies. In the analyses of alveolar carbon dioxide tension at 30 minutes and four hours (1.2.2 and 1.2.4), Wiener 1977b showed a greater effect size in favour of naloxone compared to the other studies included in these analyses. The same was true for analyses of alveolar ventilation at 30 minutes and four hours.

Figure 2. Forest plot of comparison: I Naloxone versus placebo or no drug, outcome: I.I Expired carbon dioxide output (mL/kg/min).

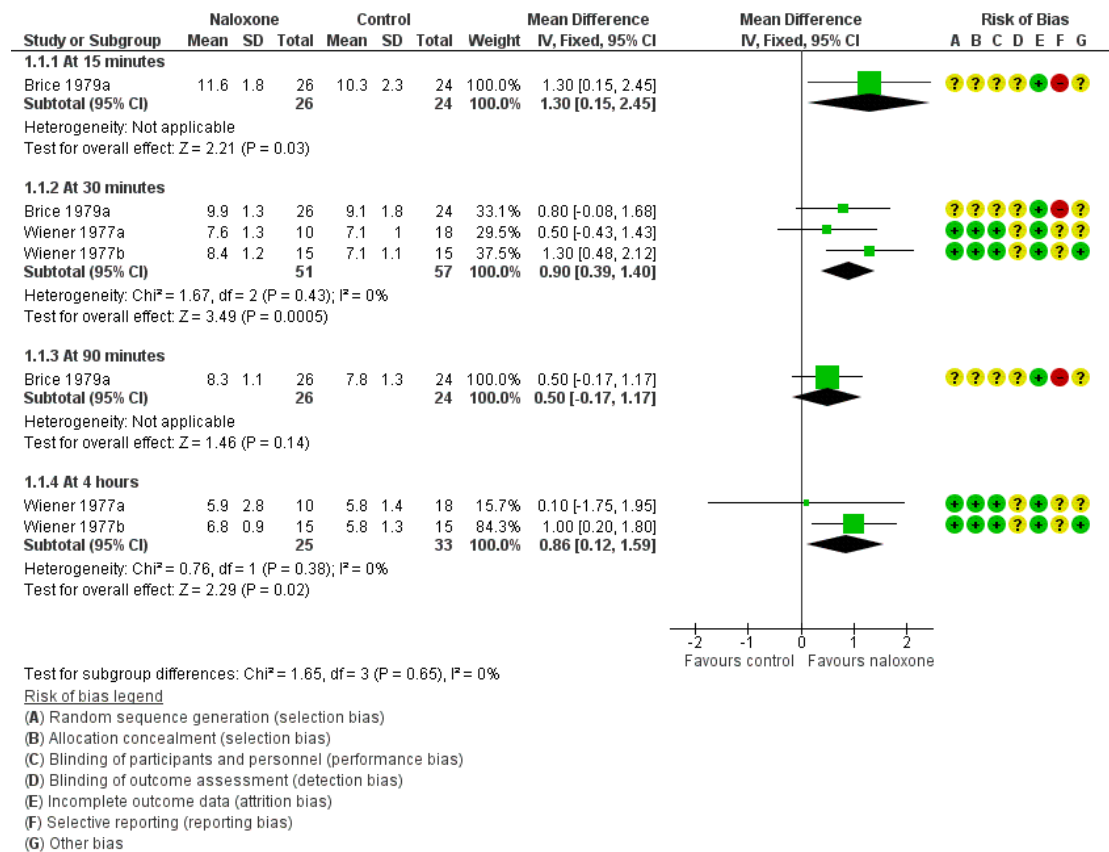


Figure 3. Forest plot of comparison: I Naloxone versus placebo or no drug, outcome: 1.2 Alveolar carbon dioxide tension (kPa).

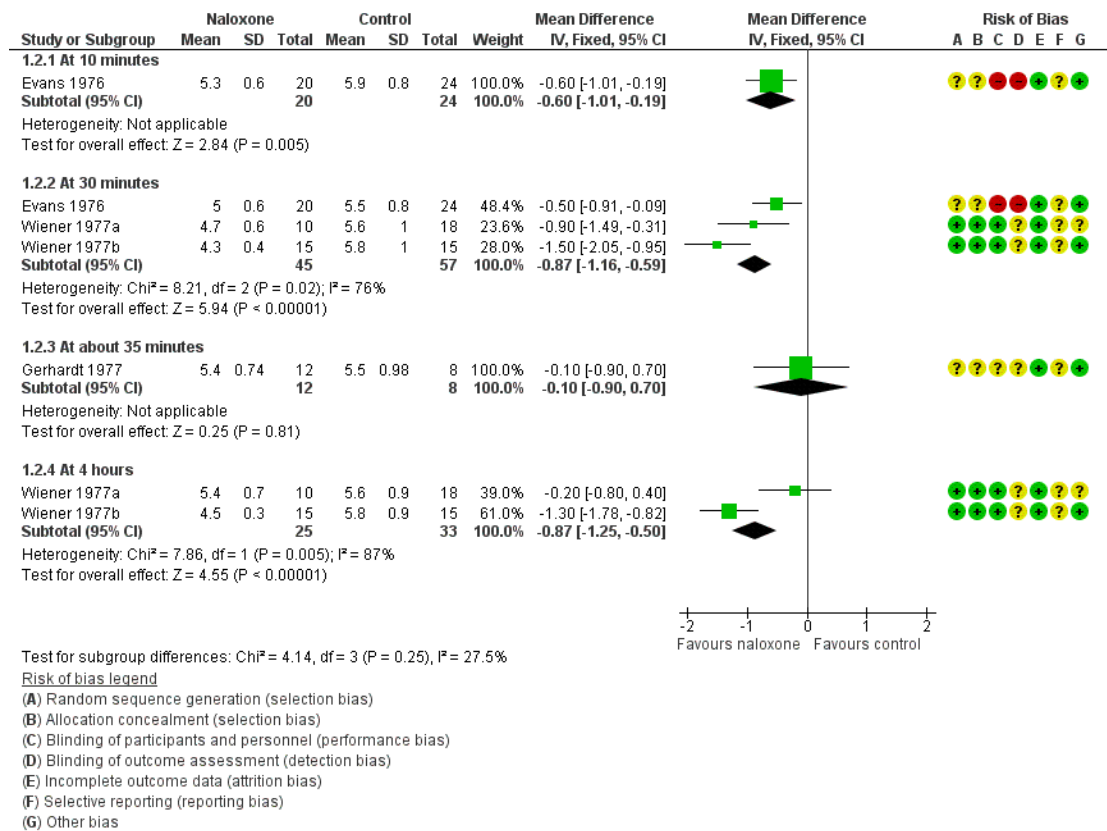
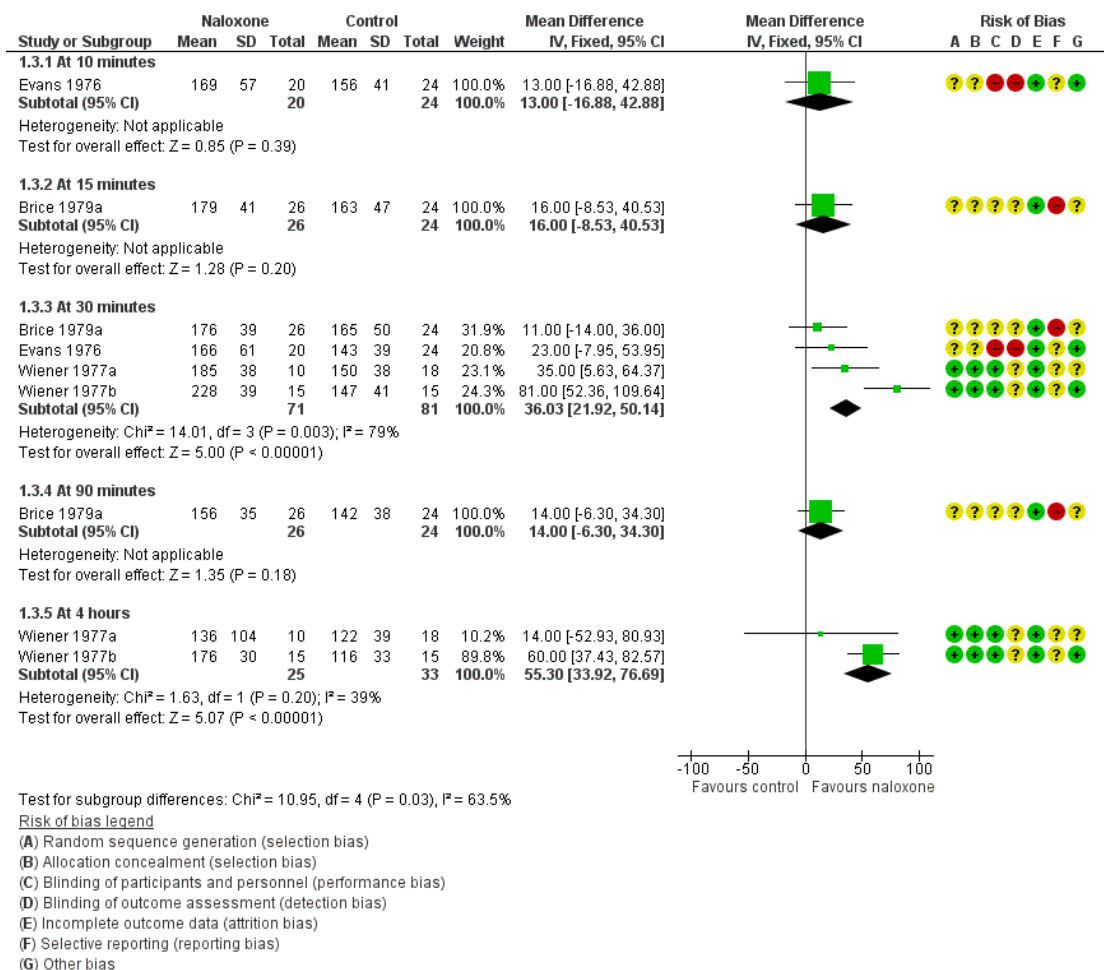


Figure 4. Forest plot of comparison: I Naloxone versus placebo or no drug, outcome: 1.3 Alveolar ventilation (mL/kg/minute).



Receipt of assisted ventilation in the neonatal period:

Not reported.

Days from birth to establish full oral feeds independently of parenteral fluids or nutrition or of enteral tube feeding:

Not reported.

Receipt of endotracheal intubation for respiratory support:

Not reported.

Features of opioid withdrawal:

The studies that reported the Scanlon Behavioural Score (Bonta 1979; Brice 1979a) and the Brazelton Neonatal Behavioural Assessment Score (Brice 1979a; Welles 1984) did not find any statistically significant differences. One trial reported the Broussard Neonatal Perception Inventory at 72 hours and found statistically significantly “less optimal behaviour” in the naloxone group (Welles 1984). Standard deviations were not reported in any of these studies. Wiener 1977b found that the time taken to habitu-

Duration of assisted ventilation:

Not reported.

Duration of endotracheal intubation: not reported.

ate to a sound-specific stimulus within the first 48 hours was statistically significantly lower in infants who received intramuscular naloxone versus placebo. [Wiener 1977a](#) stated that there were no “important differences” in habituation to auditory stimulus between infants who received intravenous naloxone versus placebo.

Seizures in the neonatal period:

Not reported.

Subgroup analyses

Dose of naloxone < 0.1 mg/kg body weight:

All of the included trials used this dose.

Dose of naloxone ≥ 0.1 mg/kg body weight:

None of the included trials used this dose.

Sensitivity analyses

Only one trial report was assessed as having an overall ‘low risk of bias’ defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and < 10% loss to follow-up ([Bonta 1979](#)). Data from this trial were not included in any of the meta-analyses.

DISCUSSION

Summary of main results

We identified nine small trials that compared naloxone versus placebo or no drug for treating newborn infants who had been exposed to maternal opioid analgesia prior to delivery. Our up-date search in 2018 identified no trials investigating naloxone in this context. The trials evaluated the effect of naloxone on infants exposed to opioid analgesia in labour. None examined the use of naloxone in infants who had been exposed to opioid in utero during pregnancy, for example, due to maternal opioid-dependence. None of the included trials provided any data on any of the primary outcomes of this review, that is, maternal separation (need for neonatal unit admission), effect on breastfeeding, and neurodevelopment beyond infancy. With regard to secondary outcome measures, most trials only reported measures of respiratory function

and neurological behaviour in the first 48 hours after birth. The analyses of measures of alveolar carbon dioxide tension and alveolar ventilation were affected by statistical heterogeneity caused by one study showing greater effect sizes in favour of naloxone ([Wiener 1977b](#)). This could be attributed to the greater dose of naloxone used in this study and possibly also to the fact that naloxone was given via the intramuscular route in this study (compared to intravenous delivery in all other studies). When given intravenously, naloxone is absorbed more effectively but has a shorter half-life compared with intramuscular administration ([Perlman 2010](#)).

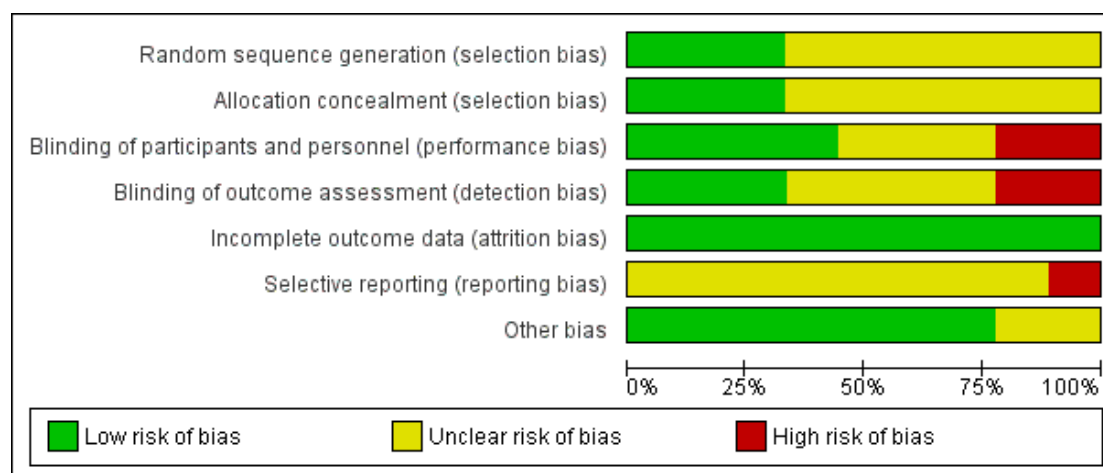
Overall completeness and applicability of evidence

The trials provided some evidence that infants who received naloxone had higher indices of alveolar ventilation, higher expired carbon dioxide levels, and lower alveolar carbon dioxide tensions than control infants. The clinical significance of these findings is unclear since the infants recruited to the trials did not appear to have been selected because of cardiorespiratory depression. Infants with low Apgar scores for up to five minutes were not eligible for inclusion in two trials ([Bonta 1979](#); [Welles 1984](#)). There were no trial data that assessed whether treatment with naloxone affected the need for, or the duration of, mechanical respiratory support including positive-pressure ventilation. All of the included trials were conducted over 30 years ago. The evidence is likely to be of limited relevance in the clinical context for which naloxone is recommended by the ILCOR, that is, for opioid-exposed newborn infants with respiratory depression despite appropriate ventilation ([Kattwinkel 2010](#); [Niermeyer 2001](#); [Perlman 2010](#)). The ILCOR Consensus on Science rates neurodevelopmental measures as a critical outcome, reflecting the high importance clinicians, policy makers, and parents place on this outcome. None of the trials included in this review reported any neurodevelopmental measures beyond infancy.

Quality of the evidence

All of the trials were small and had various methodological weaknesses including uncertain allocation concealment that may have biased their findings and the findings of this review ([Figure 5](#)). Ascertainment or surveillance biases may also be present since caregivers and clinicians in some of the trials were aware of the allocated intervention. Although follow-up assessment was complete in the trials, none assessed outcomes beyond the first few days after birth.

Figure 5. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Potential biases in the review process

Following standard Cochrane methods, we tried to minimise the risk of biases introduced during the review process. The literature search was conducted by an information specialist with the aim to identify and retrieve all relevant evidence published since the last update of this review in 2012. We searched conference abstracts and reference lists of potentially eligible publications. There remains a risk that studies could have been missed due to indexing errors in the databases. Throughout the review process, we followed methods to minimise the risk of reviewer error and bias (study selection carried out independently and in duplicate).

Agreements and disagreements with other studies or reviews

The 2010 ILCOR Consensus on Science ([Kattwinkel 2010](#); [Perlman 2010](#)) does not recommend naloxone as part of the initial resuscitation of newborn infants. This recommendation is based largely on the same body of evidence as this review. The current ILCOR Consensus on Science published in 2015 ([Perlman 2015](#)) does not mention naloxone at all, reflecting the lack of new evidence in this area.

AUTHORS' CONCLUSIONS

Implications for practice

The available trial data do not provide any evidence that administration of naloxone to infants exposed in utero to opioid during

delivery affects any important outcomes. The efficacy and safety of naloxone for infants chronically exposed in utero to opioids in opioid-dependent women has not been assessed.

Implications for research

Clinicians and service-users may consider it appropriate to undertake a randomised controlled trial to determine if naloxone confers any important benefits to newborn infants with cardiorespiratory or neurological depression that may be due to intrauterine exposure to opioids. This trial should assess outcomes that are relevant to the infant, family, and caregivers, such as the need for admission to a neonatal unit for ongoing respiratory support. In view of the concerns that naloxone may interfere with the role of endogenous opioids in neuroendocrine programming and on behaviour ([De Castro 1993](#); [Smotherman 1992](#); [Szeto 1995](#)), follow-up assessment beyond infancy should determine neurodevelopmental outcomes which have been judged to be of critical importance by ILCOR ([Perlman 2015](#)).

There are no trials concerning the use of naloxone for the treatment of infants that were chronically exposed to opioids in utero, most likely due to concerns that administration of naloxone might cause seizures in these infants ([AAP 1998](#); [Gibbs 1989](#)).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bonta 1979

Methods	Randomised controlled trial	
Participants	43 term newborn infants whose mothers had received routine narcotic analgesia within 6 hours of delivery. Infants delivered in breech presentation or by Caesarean section, and infants with Apgar score less than 6 at 1 minute, were excluded	
Interventions	1. Intramuscular naloxone (0.02 mg/kg body weight): n = 22 2. Placebo (normal saline): n = 21	
Outcomes	Apgar score at 5 minutes, capillary blood gas values at 1, 2 and 4 hours of life, neurobehavioural assessment at 1, 4, and 24 hours	
Notes	NICU, North America, late 1970s	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated in pharmacy to produce sequentially numbered ampoules containing either naloxone or placebo
Allocation concealment (selection bias)	Low risk	Sequentially numbered ampoules (unable to predict whether naloxone or placebo)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled study using sequentially numbered ampoules - personnel unlikely to have been aware of infants' group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The testers were not aware of which infants received naloxone or placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete ascertainment of outcomes
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect any other bias

Brice 1979a

Methods	Randomised controlled trial
Participants	50 term newborn infants whose mothers had received intramuscular pethidine within 4 hours of delivery
Interventions	1. Naloxone administered via the umbilical vein (0.01 or 0.02 mg/kg body weight): n = 26 2. No drug: n = 24
Outcomes	Time to sustained respiration, expired carbon dioxide output, and alveolar ventilation up to 24 hours of life, Brazelton Neonatal Behavioral Assessment Score and Scanlon Behavioral Score within the first 24 hours of life
Notes	NICU, United Kingdom, late 1970s

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Divided at random", no further details reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors blinded for Scanlon developmental assessment (but results not reported for this outcome), no further details reported on blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	High risk	"The results for the serial blood-gas analyses, the Brazelton and Scanlon scores ... are not presented in full. These may be obtained from [the corresponding author] on request."
Other bias	Unclear risk	Study was supported by a grant from Winthrop Laboratories (pharmaceutical company that manufactured the intervention)

Dick 1978a

Methods	Randomised controlled trial
Participants	40 newborn infants, of unspecified gestation, whose mothers had been given intravenous pethidine in labour
Interventions	1. Naloxone, via the umbilical vein immediately after birth (0.02 mg/kg): n = 10 2. Naloxone (0.03 mg/kg): n = 10 3. Naloxone (0.04 mg/kg): n = 10 4. No drug: n = 10
Outcomes	Capillary blood gas pH and partial pressure of carbon dioxide and of oxygen at 1, 5, 10, 30, 60 and 120 minutes of life
Notes	NICU, Germany, late 1970s

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly distributed", no further details reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect any other bias

Dick 1978b

Methods	Randomised controlled trial
Participants	30 newborn infants, of unspecified gestation, whose mothers had been given intravenous pethidine in labour

Dick 1978b (Continued)

Interventions	1. Naloxone, via the umbilical vein immediately after birth (either 0.04 mg/kg or 0.04 mg total): n = 20 2. Placebo: n = 10
Outcomes	Capillary blood gas pH, partial pressure of carbon dioxide and of oxygen, and calculated base excess at 1, 5, 10, 30, 60 and 120 minutes of life
Notes	NICU, Germany, late 1970s

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly distributed", no further details reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo and the varying amounts of Naloxone were distributed in equal amounts and thus indistinguishable"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Examiner and follow-up examiner were not informed about the agent or the dose"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect any other bias

Evans 1976

Methods	Randomised controlled trial
Participants	44 newborn infants, of gestation 38 to 42 weeks, delivered spontaneously or by forceps, whose mothers had been given pethidine in labour
Interventions	1. Naloxone administered via the umbilical vein at 1 minute of age (0.04 mg total): n = 20 2. No drug: n = 24
Outcomes	Time to first breath, time to onset of sustained respiration, Apgar score at 5 minutes, alveolar carbon dioxide tension, alveolar ventilation, and ventilation rate at 10 minutes and 30 minutes of life

Evans 1976 (Continued)

Notes	NICU, Wales, mid 1970s	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as “randomly allocated”, no further details reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect any other bias

Gerhardt 1977

Methods	Randomised controlled trial	
Participants	20 term newborn infants, born vaginally, whose mothers had received intravenous pethidine within 3 hours of delivery	
Interventions	1. Intramuscular naloxone at 30 minutes of life (0.01 mg/kg): n = 14 2. Placebo: n = 10	
Outcomes	Respiratory rate, tidal volume, minute ventilation, end-tidal carbon dioxide tension, and the ventilatory response to inhalation of 4% carbon dioxide	
Notes	NICU, North America, mid 1970s	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Gerhardt 1977 (Continued)

Random sequence generation (selection bias)	Unclear risk	“By random number ... infants were selected”, no further details reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled study but unclear if personnel were aware of infants’ allocation to groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete follow-up but 2 infants in each group were excluded post-randomisation because “lung compliance values changed more than 25% between the two determinations”
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect any other bias

Welles 1984

Methods	Randomised controlled trial	
Participants	27 newborn infants, of gestation 38 to 42 weeks, whose mothers had received pethidine during labour. Infants with Apgar scores less than 8 at 1 minute, or less than 9 at 5 minutes were not eligible for inclusion	
Interventions	1. Naloxone at about 1 hour of age (0.1 mg total, presumed intramuscularly, but this was not stated explicitly): n = 14 2. Placebo (normal saline): n = 13	
Outcomes	Brazelton Neonatal Behavioral Assessment Score at 12-24 hours of life and after a further 48 hours, and the Broussard Neonatal Perception Inventory after the second Brazelton assessment	
Notes	NICU, Sweden, early 1980s	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Welles 1984 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect any other bias

Wiener 1977a

Methods	Randomised controlled trial
Participants	28 newborn infants, of gestation 38 to 42 weeks, whose mothers had been given pethidine in labour
Interventions	1. Naloxone administered via the umbilical vein at 1 minute of age (0.04 mg total): n = 10 2. Normal saline placebo: n = 18
Outcomes	Alveolar carbon dioxide tension, carbon dioxide excretion, alveolar ventilation, feeding behaviour, and habituation to a sound-specific stimulus up to 48 hours of life
Notes	NICU, Wales, mid 1970s

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation in pharmacy
Allocation concealment (selection bias)	Low risk	Coded ampoules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Naloxone or normal saline were "chosen blind at random"

Wiener 1977a (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Likely to have been blinded but not stated explicitly either way in the paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Unclear risk	The study was stopped early because the randomisation code was broken after 28 infants had been enrolled

Wiener 1977b

Methods	Randomised controlled trial
Participants	30 newborn infants, of gestation 38 to 42 weeks, whose mothers had been given pethidine in labour
Interventions	1. Intramuscular naloxone at 1 minute of age (0.2 mg total): n = 15 2. Intramuscular normal saline placebo: n = 15
Outcomes	Alveolar carbon dioxide tension, carbon dioxide excretion, alveolar ventilation, feeding behaviour (mean sucking frequencies and pressures, and mean milk consumption), and habituation to a sound-specific stimulus up to 48 hours of life
Notes	NICU, Wales, mid 1970s

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation in pharmacy
Allocation concealment (selection bias)	Low risk	Coded ampoules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Naloxone or normal saline were "chosen blind at random"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Likely to have been blinded but not stated explicitly either way in the paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

Wiener 1977b (Continued)

Selective reporting (reporting bias)	Unclear risk	No protocol (though no reason to suspect selective reporting)
Other bias	Low risk	No reason to suspect other bias

NICU: Neonatal intensive care unit

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brice 1979b	This report of pharmacokinetic data in infants who received either intravenous or intramuscular naloxone was unlikely to be a randomised comparison
Martin 1972	This report was unlikely to be a randomised controlled trial

DATA AND ANALYSES

Comparison 1. Naloxone versus placebo or no drug

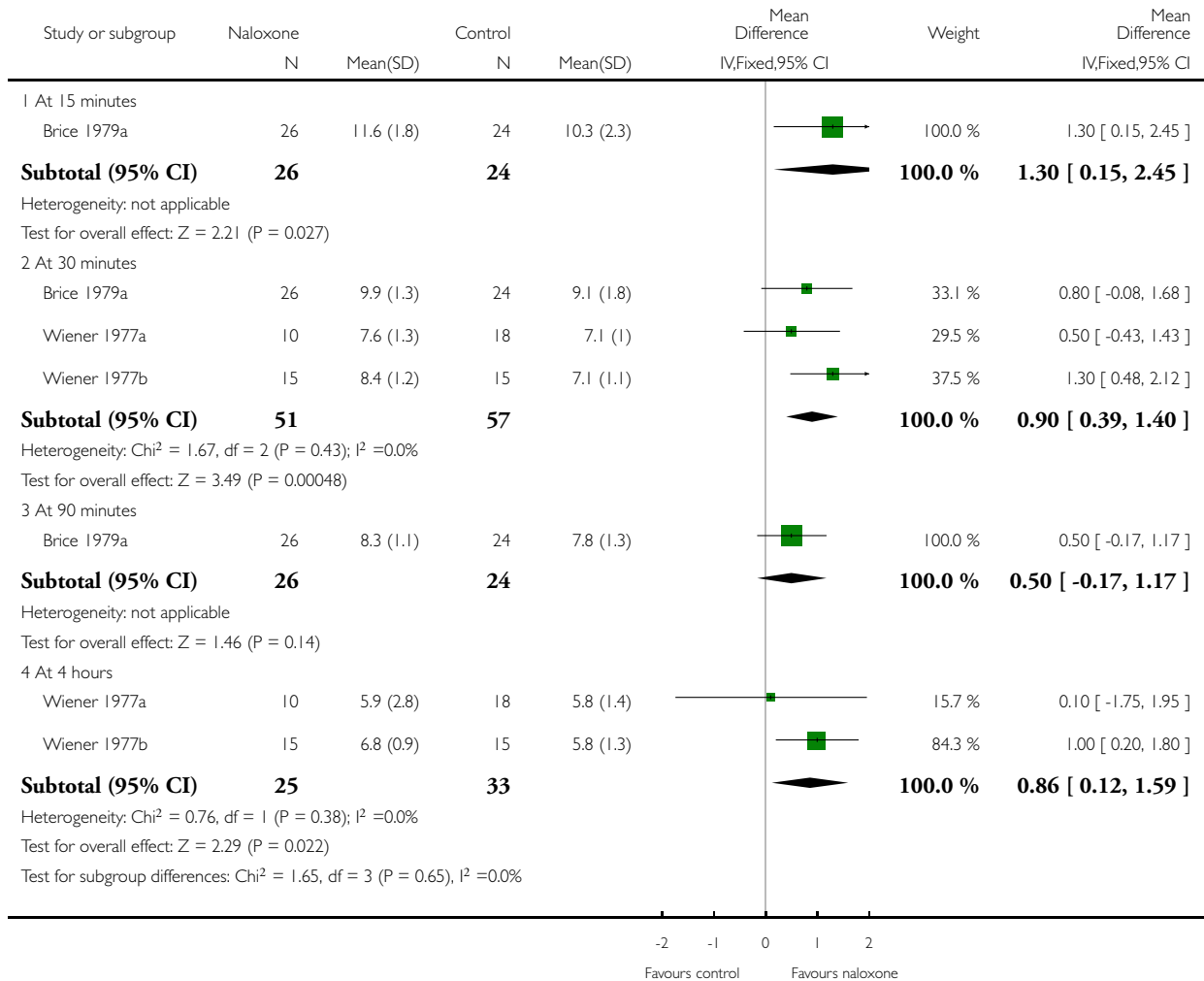
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Expired carbon dioxide output (mL/kg/min)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 15 minutes	1	50	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.15, 2.45]
1.2 At 30 minutes	3	108	Mean Difference (IV, Fixed, 95% CI)	0.90 [0.39, 1.40]
1.3 At 90 minutes	1	50	Mean Difference (IV, Fixed, 95% CI)	0.50 [-0.17, 1.17]
1.4 At 4 hours	2	58	Mean Difference (IV, Fixed, 95% CI)	0.86 [0.12, 1.59]
2 Alveolar carbon dioxide tension (kPa)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 10 minutes	1	44	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.01, -0.19]
2.2 At 30 minutes	3	102	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-1.16, -0.59]
2.3 At about 35 minutes	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.90, 0.70]
2.4 At 4 hours	2	58	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-1.25, -0.50]
3 Alveolar ventilation (mL/kg/minute)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 10 minutes	1	44	Mean Difference (IV, Fixed, 95% CI)	13.0 [-16.88, 42.88]
3.2 At 15 minutes	1	50	Mean Difference (IV, Fixed, 95% CI)	16.0 [-8.53, 40.53]
3.3 At 30 minutes	4	152	Mean Difference (IV, Fixed, 95% CI)	36.03 [21.92, 50.14]
3.4 At 90 minutes	1	50	Mean Difference (IV, Fixed, 95% CI)	14.0 [-6.30, 34.30]
3.5 At 4 hours	2	58	Mean Difference (IV, Fixed, 95% CI)	55.30 [33.92, 76.69]

Analysis 1.1. Comparison 1 Naloxone versus placebo or no drug, Outcome 1 Expired carbon dioxide output (mL/kg/min).

Review: Naloxone for opioid-exposed newborn infants

Comparison: 1 Naloxone versus placebo or no drug

Outcome: 1 Expired carbon dioxide output (mL/kg/min)

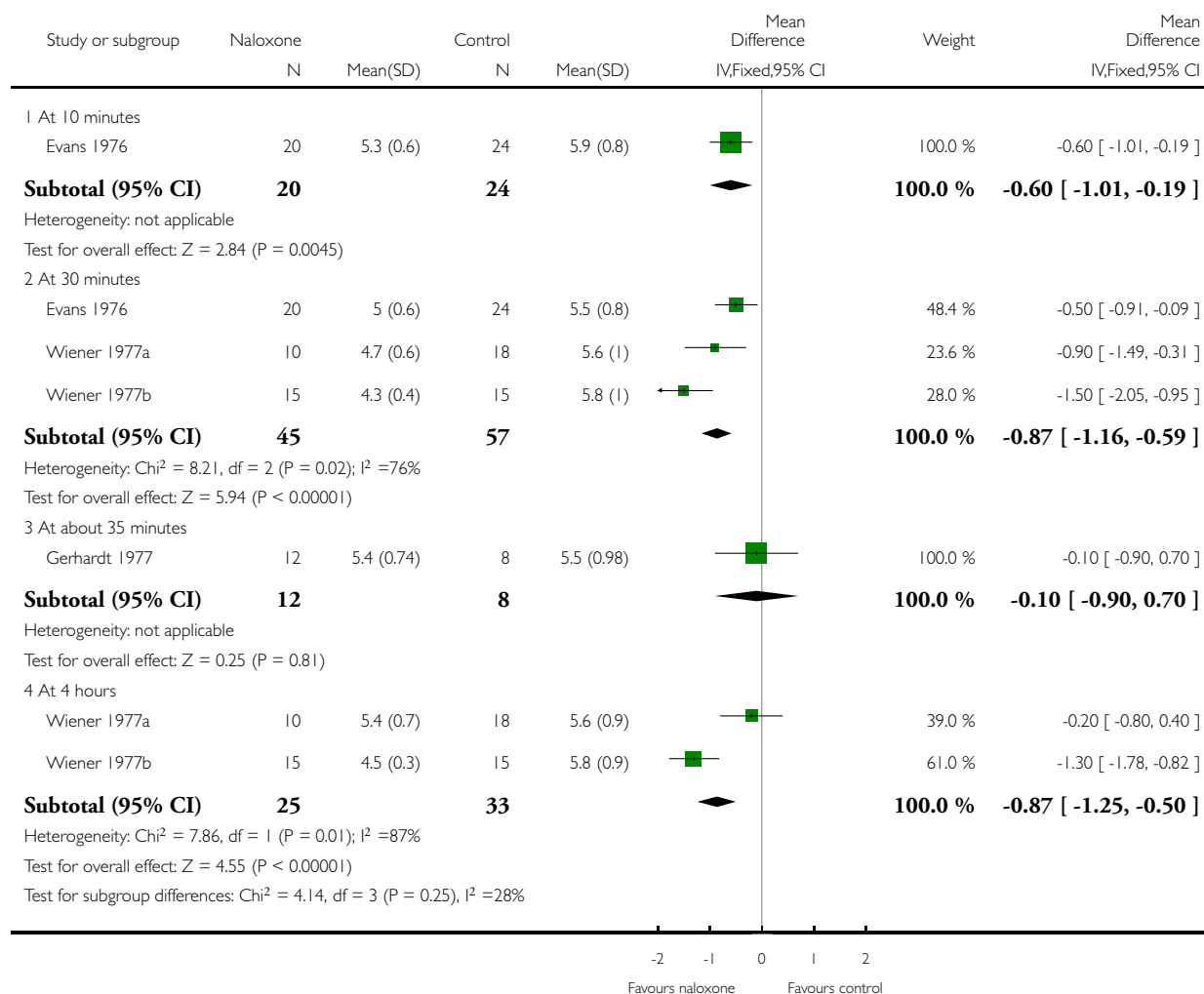


Analysis 1.2. Comparison 1 Naloxone versus placebo or no drug, Outcome 2 Alveolar carbon dioxide tension (kPa).

Review: Naloxone for opioid-exposed newborn infants

Comparison: 1 Naloxone versus placebo or no drug

Outcome: 2 Alveolar carbon dioxide tension (kPa)

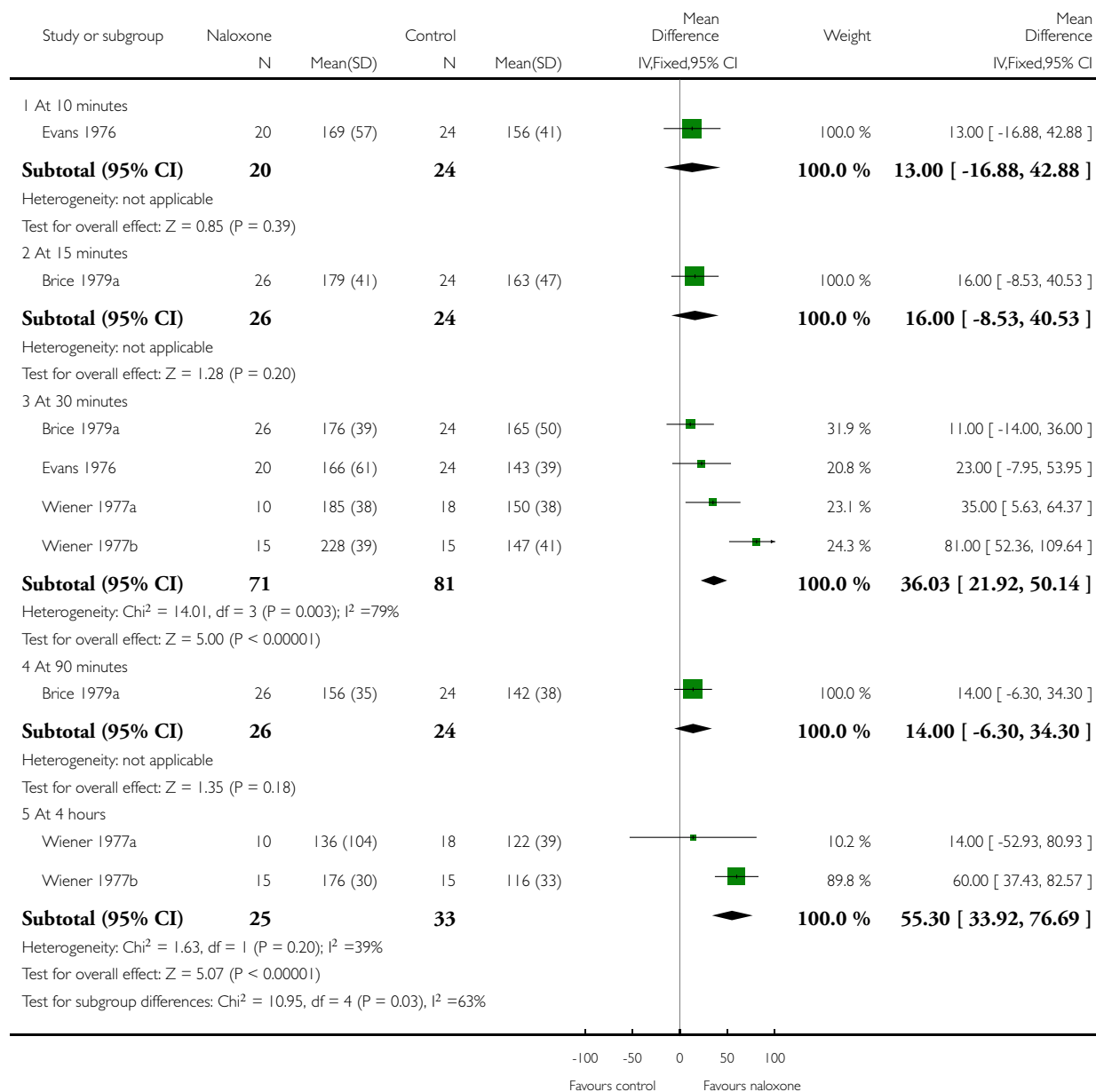


Analysis 1.3. Comparison 1 Naloxone versus placebo or no drug, Outcome 3 Alveolar ventilation (mL/kg/minute).

Review: Naloxone for opioid-exposed newborn infants

Comparison: 1 Naloxone versus placebo or no drug

Outcome: 3 Alveolar ventilation (mL/kg/minute)



APPENDICES

Appendix I. Electronic search strategy

Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

Wiley <http://onlinelibrary.wiley.com/>

Issue 1 of 12, January 2018

Searched on: 20th February 2018

Records retrieved: 14

#1 MeSH descriptor: [Infant, Newborn] explode all trees 15665

#2 MeSH descriptor: [Premature Birth] this term only 597

#3 (neonat* or neo next nat*):ti,ab 14017

#4 (newborn* or new next born* or newly next born*):ti,ab 6237

#5 (preterm or preterms or pre next term or pre next terms):ti,ab 9039

#6 (preemie* or premie or premies):ti,ab 21

#7 (prematur* near/3 (birth* or born or deliver*)):ti,ab 1118

#8 (low near/3 (birthweight* or birth next weight*)):ti,ab 3505

#9 (lbw or vlbw or elbw):ti,ab 1221

#10 infan*:ti,ab 27709

#11 (baby or babies):ti,ab 4644

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 44720

#13 MeSH descriptor: [Naloxone] explode all trees 1833

#14 naloxone:ti,ab 1826

#15 narcen:ti,ab 5

#16 MeSH descriptor: [Narcotic Antagonists] this term only 1129

#17 ((narcotic or opiate or opioid) near/3 antagonist*):ti,ab 1031

#18 #13 or #14 or #15 or #16 or #17 3280

#19 #12 and #18 76

#20 #12 and #18 in Trials 68

#21 #12 and #18 Publication Year from 2007 to 2018 14

Line #20 shows the number of hits in CENTRAL only.

Key

MeSH descriptor = indexing term (MeSH heading)

* = truncation

:ti,ab = terms in either title or abstract fields

NEAR/3 = terms within three words of each other (any order)

NEXT = terms are next to each other

CINAHL

via EBSCO <http://www.ebsco.com/>

Inception to 19th February 2018

Searched on: 20th February 2018

Records retrieved: 83

S1 MH "Infant, Newborn+" 107,105

S2 MH "Infant, Low Birth Weight+" 10,646

S3 MH "Infant, Premature" 17,476

S4 (MH "Childbirth, Premature") 7,235

S5 TI (neonat* or neo-nat*) OR AB (neonat* or neo-nat*) 45,560

S6 TI (newborn* or new-born* or newly N1 born*) OR AB (newborn* or new-born* or newly N1 born*) 21,724

S7 TI (preterm or preterms or pre-term or pre-terms) OR AB (preterm or preterms or pre-term or pre-terms) 22,267

S8 TI (preemie* or premie or premies) OR AB (preemie* or premie or premies) 239

S9 TI (prematur* N3 (birth* or born or deliver*)) OR AB (prematur* N3 (birth* or born or deliver*)) 3,179

S10 TI (low N3 (birthweight* or birth-weight*)) OR AB (low N3 (birthweight* or birth-weight*)) 8,753

S11 TI (lbw or vlbw or elbw) OR AB (lbw or vlbw or elbw) 2,359
 S12 TI infan* OR AB infan* 79,927
 S13 TI (baby or babies) OR AB (baby or babies) 23,527
 S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 190,257
 S15 (MH "Naloxone+") 3,344
 S16 TI naloxone OR AB naloxone 1,874
 S17 TI narkan OR AB narkan 38
 S18 (MH "Narcotic Antagonists") 1,598
 S19 TI (((narcotic or opiate or opioid) N3 antagonist*)) OR AB (((narcotic or opiate or opioid) N3 antagonist*)) 796
 S20 S15 OR S16 OR S17 OR S18 OR S19 4,922
 S21 S14 AND S20 140
 S22 S14 AND S20 Limiters - Publication Year: 2007-2018 83

Key

MH = indexing term (CINAHL heading)
 + = exploded CINAHL heading
 * = truncation
 TI = words in the title
 AB = words in the abstract
 N3 = terms within three words of each other (any order)

Embase

OvidSP <http://ovidsp.ovid.com/>

1974 to 2018 February 18

Searched on: 19th February 2018

Records retrieved: 50

A search strategy developed by Lefebvre et. al. to identify randomised trials in Embase was used to limit retrieval to clinical trials (lines 23-37) (Lefebvre 2008).

1 exp infant/ (983099)
 2 newborn/ (535610)
 3 prematurity/ (91829)
 4 premature labor/ (40137)
 5 exp low birth weight/ (53021)
 6 (neonat\$ or neo nat\$).ti.ab. (302625)
 7 (newborn\$ or new born\$ or newly born\$).ti.ab. (184612)
 8 (preterm or preterms or pre term or pre terms).ti.ab. (86396)
 9 (preemie\$ or premie or premies).ti.ab. (214)
 10 (premat\$ adj3 (birth\$ or born or deliver\$)).ti.ab. (18958)
 11 (low adj3 (birthweight\$ or birth weight\$)).ti.ab. (38393)
 12 (lbw or vlbw or elbw).ti.ab. (9710)
 13 infan\$.ti.ab. (460096)
 14 (baby or babies).ti.ab. (85499)
 15 or/1-14 (1360576)
 16 naloxone/ (39568)
 17 naltrexone/ (13293)
 18 naloxone.ti.ab. (25894)
 19 narkan.ti.ab. (120)
 20 narcotic antagonist/ (2171)
 21 ((narcotic or opiate or opioid) adj3 antagonist\$).ti.ab. (13795)
 22 16 or 17 or 18 or 19 or 20 or 21 (58022)
 23 random\$.ti.ab. (1269278)
 24 factorial\$.ti.ab. (32048)
 25 crossover\$.ti.ab. (64838)
 26 cross-over\$.ti.ab. (28769)
 27 placebo\$.ti.ab. (268419)

28 (doubl\$ adj blind\$).ti,ab. (186242)
 29 (singl\$ adj blind\$).ti,ab. (20605)
 30 assign\$.ti,ab. (330112)
 31 allocat\$.ti,ab. (123986)
 32 volunteer\$.ti,ab. (228781)
 33 Crossover Procedure/ (54337)
 34 double blind procedure/ (146460)
 35 Randomized Controlled Trial/ (487494)
 36 single blind procedure/ (30408)
 37 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (1963083)
 38 15 and 22 and 37 (141)
 39 animal/ (1835634)
 40 exp animal experiment/ (2167842)
 41 nonhuman/ (5322101)
 42 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
 (5689708)
 43 39 or 40 or 41 or 42 (8403753)
 44 exp human/ (19255041)
 45 human experiment/ (396693)
 46 44 or 45 (19256570)
 47 43 not (43 and 46) (6322301)
 48 38 not 47 (119)
 49 limit 48 to yr="2007 -Current" (50)

Key:

/ = indexing term (EMTREE heading)

exp = exploded EMTREE heading

\$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

.sh. = terms in the EMTREE heading field

Maternity and Infant Care

OvidSP <http://ovidsp.ovid.com/>

1971 to December 2017

Searched on: 20th February 2018

Records retrieved: 65

1 (neonat\$ or neo nat\$).mp. (42157)
 2 (newborn\$ or new born\$ or newly born\$).mp. (38013)
 3 (preterm or preterms or pre term or pre terms).mp. (23364)
 4 (preemie\$ or premie or premies).mp. (50)
 5 (prematur\$ adj3 (birth\$ or born or deliver\$)).mp. (6532)
 6 (low adj3 (birthweight\$ or birth weight\$)).mp. (10998)
 7 (lbw or vlbw or elbw).mp. (2765)
 8 infan\$.mp. (82242)
 9 (baby or babies).mp. (27270)
 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (117850)
 11 naloxone.mp. (74)
 12 Naltrexone.mp. (10)
 13 narkan.mp. (1)
 14 ((narcotic or opiate or opioid) adj3 antagonist\$).mp. (20)
 15 11 or 12 or 13 or 14 (91)
 16 10 and 15 (65)

Key

\$ = truncation

.mp. = multi-purpose field search - includes terms in either title, abstract, keyword heading, name of substance, original title or subject heading fields

adj3 = terms within three words of each other (any order)

MEDLINE

OvidSP <http://ovidsp.ovid.com/>

1946 to February Week 2 2018

Searched on: 19th February 2018

Records retrieved: 89

The Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE (sensitivity-maximizing version) was used to limit retrieval to clinical trials (lines 19-29) (Lefebvre 2011).

1 exp Infant, Newborn/ (560906)

2 Premature Birth/ (10524)

3 (neonat\$ or neo nat\$).ti,ab. (214766)

4 (newborn\$ or new born\$ or newly born\$).ti,ab. (140975)

5 (preterm or preterms or pre term or pre terms).ti,ab. (55474)

6 (preemie\$ or premie or premies).ti,ab. (137)

7 (prematur\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (12830)

8 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (28169)

9 (lbw or vlbw or elbw).ti,ab. (6466)

10 infan\$.ti,ab. (360691)

11 (baby or babies).ti,ab. (56440)

12 or/1-11 (903657)

13 exp Naloxone/ (23951)

14 naloxone.ti,ab,rn. (24723)

15 narkan.ti,ab,rn. (57)

16 Narcotic Antagonists/ (12351)

17 ((narcotic or opiate or opioid) adj3 antagonist\$).ti,ab. (11217)

18 or/13-17 (35523)

19 randomized controlled trial.pt. (453101)

20 controlled clinical trial.pt. (92131)

21 randomized.ab. (352150)

22 placebo.ab. (170252)

23 drug therapy.fs. (1991268)

24 randomly.ab. (244938)

25 trial.ab. (364753)

26 groups.ab. (1531866)

27 or/19-26 (3828607)

28 exp animals/ not humans/ (4424434)

29 27 not 28 (3265481)

30 12 and 18 and 29 (233)

31 limit 30 to yr="2007 -Current" (89)

Key

/ = indexing term (MeSH heading)

exp = exploded MeSH heading

\$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

.pt.= terms in the publication type field

.fs.= floating subheading

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily)

OvidSP <http://ovidsp.ovid.com/>

16th February 2018

Searched on: 19th February 2018

Records retrieved: 27

1 exp Infant, Newborn/ (436)

2 Premature Birth/ (16)

3 (neonat\$ or neo nat\$).ti,ab. (19923)

4 (newborn\$ or new born\$ or newly born\$).ti,ab. (10342)

5 (preterm or preterms or pre term or pre terms).ti,ab. (7080)

6 (preemie\$ or premie or premies).ti,ab. (8)

7 (prematu\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (1180)

8 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (2673)

9 (lbw or vlbw or elbw).ti,ab. (727)

10 infan\$.ti,ab. (31472)

11 (baby or babies).ti,ab. (6278)

12 or/1-11 (56812)

13 exp Naloxone/ (13)

14 naloxone.ti,ab,rn. (993)

15 narkan.ti,ab,rn. (6)

16 Narcotic Antagonists/ (13)

17 ((narcotic or opiate or opioid) adj3 antagonist\$).ti,ab. (526)

18 or/13-17 (1307)

19 12 and 18 (27)

PubMed

<http://www.ncbi.nlm.nih.gov/pubmed/>

Searched on: 20th February 2018

Records retrieved: 246

The Cochrane highly sensitive search strategy for identifying randomized trials in PubMed (sensitivity-maximizing version) was used to limit retrieval to clinical trials (Lefebvre 2011).

Search (((((((((((((((("Infant, Newborn"[Mesh])) OR ("Premature Birth"[Mesh])) OR (((neonat*[Title/Abstract]) OR neo nat*[Title/Abstract]) OR neo-nat*[Title/Abstract])) OR (((newborn*[Title/Abstract]) OR new born*[Title/Abstract]) OR new-born*[Title/Abstract]) OR newly born*[Title/Abstract]) OR newly-born*[Title/Abstract])) OR (((preterm[Title/Abstract]) OR preterms[Title/Abstract]) OR pre term[Title/Abstract]) OR pre-term[Title/Abstract]) OR pre terms[Title/Abstract]) OR pre-terms[Title/Abstract])) OR (((preemie*[Title/Abstract]) OR premie[Title/Abstract]) OR premies[Title/Abstract])) OR ((prematu*[Title/Abstract]) AND birth*[Title/Abstract])) OR ((prematu*[Title/Abstract]) AND born[Title/Abstract])) OR ((prematu*[Title/Abstract]) AND deliver*[Title/Abstract])) OR ((low[Title/Abstract]) AND birthweight*[Title/Abstract])) OR ((low[Title/Abstract]) AND birth weight*[Title/Abstract])) OR ((low[Title/Abstract]) AND birth-weight*[Title/Abstract])) OR (((lbw[Title/Abstract]) OR vlbw[Title/Abstract]) OR elbw[Title/Abstract])) OR (infan*[Title/Abstract])) OR ((baby[Title/Abstract]) OR babies[Title/Abstract])) AND (((((((("Naloxone"[Mesh])) OR (naloxone)) OR (narkan)) OR ((narcotic[Title/Abstract]) AND antagonist*[Title/Abstract])) OR ((opiate[Title/Abstract]) AND antagonist*[Title/Abstract])) OR ("Narcotic Antagonists"[Mesh:noexp])) OR ((opioid[Title/Abstract]) AND antagonist*[Title/Abstract]))) AND (((((((((((randomized controlled trial[Publication Type])) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) NOT (animals[mh] NOT humans[mh]))

Key

[Mesh] = exploded indexing term (MeSH heading)

[mh] = exploded indexing term (MeSH heading)

[Mesh:NoExp] = indexing term (MeSH heading) not exploded

* = truncation

[Title/Abstract] = terms in either title or abstract fields

[Publication Type] = terms in the publication type field

[MeSH Subheading] = MeSH subheading

Trial registers

ClinicalTrials.gov

<http://www.clinicaltrials.gov/>

Searched on: 20th February 2018

Records retrieved: 5

1. Naloxone AND (infant OR infants OR newborn OR newborns OR premature OR prematurity OR neonate OR neonates OR neonatal OR preterm OR preterms OR preemie OR preemies OR premie OR premies OR birthweight OR baby OR babies) - 3 studies
2. Narcan AND (infant OR infants OR newborn OR newborns OR premature OR prematurity OR neonate OR neonates OR neonatal OR preterm OR preterms OR preemie OR preemies OR premie OR premies OR birthweight OR baby OR babies) - 2 studies

WHO International Clinical Trials Registry Platform

<http://apps.who.int/trialsearch/AdvSearch.aspx>

Searched on: 20th February 2018

Records retrieved: 9

1. Naloxone in title, clinical trials in children - 5 results
2. Naloxone in intervention field, clinical trials in children - 4 results
3. Narcan in title, clinical trials in children - 0
4. Narcan in intervention field, clinical trials in children - 0 results

EU Clinical Trials Register

<https://www.clinicaltrialsregister.eu/ctr-search/search>

Searched on: 20th February 2018

Records retrieved: 0

1. naloxone textword search, limited to newborn or preterm new born infants age filter - 0 results
2. narcan textword search, limited to newborn or preterm new born infants age filter - 0 results

Appendix 2. Risk of bias tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion, where reported, and whether missing data were balanced across

groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (\geq 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported);
- high risk (where not all the study's prespecified outcomes had been reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

Appendix 3. GRADE

GRADE considers that evidence from randomised controlled trials initially is "high" quality but that assessment may be downgraded based on consideration of any of five areas:

- design (risk of bias);
- consistency across studies;
- directness of the evidence;
- precision of estimates; and
- presence of publication bias.

This results in an assessment of the quality of a body of evidence in one of four grades:

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

WHAT'S NEW

Last assessed as up-to-date: 20 February 2018.

Date	Event	Description
9 May 2018	New search has been performed	This updates the review "Naloxone for opioid-exposed newborn infants" (Moe-Byrne 2013).
9 May 2018	New citation required but conclusions have not changed	Search updated in February 2018. No new trials added. Background and discussion updated. Risk of Bias tables updated. Summary of findings table added.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 4, 2002

Date	Event	Description
31 July 2012	New citation required but conclusions have not changed	Search updated in June 2012. No new trials added. Background and discussion updated.
10 June 2008	Amended	Converted to new review format.
14 March 2007	New search has been performed	<p>This review updates "Naloxone for narcotic-exposed newborn infants", published in the Cochrane Database of Systematic Reviews, The Cochrane Library, Issue 4, 2002 (McGuire 2002).</p> <p>Our electronic search was updated in February 2007. No new trials that fulfilled eligibility criteria were identified.</p> <p>We re-categorised studies that were previously listed as "studies awaiting assessment". Four of these were abstracts presenting data that was also presented in included substantive publications. These are now listed as secondary publications. One study was excluded</p>
18 June 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Thirimon Moe-Byrne and Jennifer Brown searched and screened the studies for inclusion, assessed the methodological quality of the trials, and extracted and entered the relevant information and data from each included study independently. All authors completed the final review.

DECLARATIONS OF INTEREST

None.

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Internal sources

- Centre for Reviews and Dissemination, University of York, UK.

External sources

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- Vermont Oxford Network, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2018 update, we made the following changes:

- Neurodevelopment promoted to primary outcome because ILCOR has ranked this as a “critical” outcome across the board in the 2015 consensus statement ([Perlman 2015](#)).
- We changed the title of the review from “opiate” to “opioid”, as a broader term. The original protocol title was “Naloxone for narcotic-exposed newborn infants”.
- We added the methodology and plan for ‘Summary of findings’ tables and GRADE recommendations, which were not included in the original protocol or the previously published review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Prenatal Exposure Delayed Effects; Naloxone [*therapeutic use]; Narcotic Antagonists [*therapeutic use]; Narcotics [*adverse effects]; Randomized Controlled Trials as Topic; Respiratory Insufficiency [chemically induced; *drug therapy]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy